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Water-soluble polymers and hydrogels are important in areas as varied as biomedicine, adhesion, membranes, and viscosity enhancement. They are possible replacements in technology and medicine for many naturally-occurring polymers. Unfortunately, relatively few of the hundreds of known synthetic polymers are soluble in water. Thus, the design and synthesis of new water-soluble polymers or hydrogels is a subject of considerable interest. This chapter is a review of an approach to this problem.

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Prepared for Publication in ACS Symposium Series

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Water-soluble synthetic polymers and hydrogels are important in areas as varied as biomedicine, adhesion, membranes, and viscosity enhancement. They are possible replacements in technology and medicine for many naturally-occurring polymers. Unfortunately, relatively few of the hundreds of known synthetic polymers are soluble in water. Thus, the design and synthesis of new water-soluble polymers or hydrogels is a subject of considerable interest. This chapter is a review of an approach to this problem that makes use of the following concepts.

Concepts Used in this Work

Water-solubility in polymers results from two influences. First, solubility in water may result from the presence of certain hydrophilic units in the polymer backbone--especially units such as -O-, -NH-, or -N= that possess lone pair electrons for hydrogen bonding to water. Second, water-solubility often results from the presence of hydrophilic side groups, such as -OH, -COONa, $-NH_2$, $-NHCH_3$, $-SO_3^-$, or -C=O, or amphiphilic units such as $-OCH_2CH_2O-$, etc. High concentrations of hydrophilic side groups may overcome a lack of hydrophilic units in the backbone, but a hydrophilic backbone is the best starting point for water-soluble polymer design.

The second concept used in this work is related to the method of polymer synthesis. Two general methods exist for bringing about variations in polymer structure: (1) The polymerization or copolymerization of different monomers, and (2) macromolecular substitution reactions in which side groups already attached to a polymer

chain are replaced by other groups (Scheme I). The first method is more widely used than the second, mainly because of the availability of a wide range of petrochemical monomers, but also because the side group replacement reactions of organic polymers are often relatively inefficient. Nevertheless, as will be demonstrated, the macromolecular substitution approach is an excellent method for the synthesis of water-soluble polymers since it allows a high degree of utilization of molecular design and either extensive or subtle structural manipulation.

The third principle is this: that one of the most effective routes to hydrogel formation is via the cross-linking of water-soluble polymers (Figure 1). Cross-links between hitherto water-soluble polymer molecules will prevent dissolution of the polymer in water, However, the cross-linked material will absorb water and swell to an extent that is defined by the number of cross-links per chain. Thus, the design of hydrogels (which are of critical importance in the field of biomedicine) depends on the development of cross-linking methods that are appropriate for side groups that impart water-solubility.

The fourth concept, that will be referred to later, concerns the stability of a water-soluble polymer or hydrogel to hydrolysis in aqueous media. In most technological applications, hydrolytic instability is considered to be a detrimental property. However, in biomedicine, hydrolytic breakdown of the polymer or a hydrogel, may be an essential requirement if the polymer must eventually "erode" as it is replaced by living cells or after its use as a drug delivery platform has been completed (Figure 2). Hydrolytic instability can often be designed into a polymer by the selection of the main chain units, the side groups, or both.

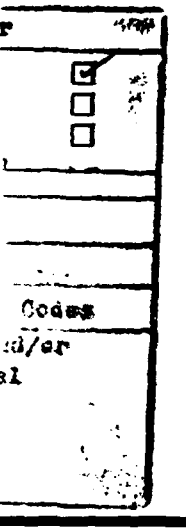
The last concept to be illustrated in this chapter is that a group of polymers known as polyphosphazenes (1) have many advantages for development as water-soluble polymers or hydrogels. The backbone is hydrophilic, the chain structure has a high

degree of flexibility, and (depending on the side groups) the backbone may be induced to undergo hydrolysis. However, the main advantage of these polymers is the ease with which water-solubilizing side groups can be linked to the chain via macromolecular substitution reactions. As will be demonstrated, the backbone is sufficiently stable to high energy radiation that X-rays, gamma rays, electron-beam, or ultraviolet irradiation can be used as a clean and effective way to crosslink the polymers through the side groups in order to generate hydrogels.

Methods of Phosphazene Polymer Synthesis

The main method for the synthesis of polyphosphazenes is illustrated in Scheme II.[1-6] It consists of a ring-opening polymerization of a heterocyclic "monomer", shown as 2, followed by replacement of the chlorine atoms in the resultant polymer (3) by organic groups through macromolecular nucleophilic substitution reactions. The chlorine replacement step can be carried out either to introduce only one type of side group or, by simultaneous or sequential substitution, to introduce two or more different types of side groups. The most important feature of this reaction is that the high reactivity of the P-Cl bonds allows all the halogen atoms to be replaced. Considering that the average chain length of polymer 3 is 15,000 repeating units, this means that 30,000 chlorine atoms are replaced per polymer chain! Bulky nucleophiles (such as aryloxide) may slow this reaction to the point that elevated temperatures may be required to allow the reaction to proceed to completion. A variation on this synthesis method, in which some of the organic groups are introduced before ring-opening polymerization, is shown in Scheme III.[7-9] Both of the routes shown in Schemes II and III were discovered and developed in our research program and have, so far, led to the synthesis of more than 300 different polyphosphazenes.

Alternative synthesis routes, that involve condensation-type processes, have been developed in other laboratories, and these are shown in Scheme IV.[10-14]



Examples of Water-Soluble Polyphosphazenes

Chart I shows six different polyphosphazenes that are soluble in water. All of them were synthesized in our laboratory via variants of the chemistry shown in Scheme II. Each has the same hydrophilic backbone structure, and all bear hydrophilic side groups. Three, and possibly four of them are stable to hydrolysis at room temperature or body temperature. Two of them (6 and 7) hydrolyze at detectable rates in neutral aqueous media at 100°C and are presumed to hydrolyze slowly at lower temperatures. The following discussion will consider each of these examples in turn, illustrating the differences and opportunities for molecular design and property optimization.

1. Poly[bis(methylamino)phosphazene] (4). This polymer was the first water-soluble polyphosphazene to be synthesized.[15] It is prepared by the addition of a THF solution of poly(dichlorophosphazene) (3) to a large excess of methylamine in the same solvent at 0°C. These reaction conditions were chosen to minimize the possibility that a -N(H)-CH_3 side unit could crosslink the chains during synthesis through reaction with a P-Cl unit or another chain. This polymer has a glass transition temperature (Tg) of 14°C.

The water-solubility of 4 is believed to be due to (a) the small size of the side groups, which exposes the skeletal nitrogen atoms to hydrogen bonding to water, and (b) strong hydrogen bonding between water and the NH units of the side groups. This polymer appears to be stable to neutral and basic aqueous media but hydrolyzes to phosphate and ammonium salts in strong acids.

Polymer 4 is sensitive to cross-linking when exposed to gamma-rays.[16] The mechanism of this process is illustrated in Scheme V. Cross-linking is believed to occur by radiation-induced, carbon-hydrogen bond cleavage, followed by cross-combination of the $NHCH_2\cdot$ radicals produced. This cross-linking process has been used to stabilize

amphiphilic membranes prepared from polyphosphazenes that contain both methylamino and fluoroalkoxy or aryloxy cosubstituent groups.[16]

2. *Poly[bis(methoxyethoxyethoxy)phosphazene] (5) ("MEEP").* One of the most interesting and potentially most useful polyphosphazenes yet synthesized is polymer 5. This polymer is prepared by the reaction of poly(dichlorophosphazene) (3) with the sodium salt of methoxyethoxyethanol in THF solution (Scheme VI).[17] Because the polymer is infinitely water-soluble at 25°C, it can be purified by dialysis.

MEEP has unusual solution properties in water, exhibiting the phenomenon known as a lower critical solution temperature ("LCST"). Polymers that possess this characteristic are soluble below a specific temperature, but become insoluble at temperatures above this point (Figure 3). MEEP has a LCST of 80°C. A number of polymers related to MEEP, but with different etheric side groups, different alkyl ether chain lengths, and different terminal alkoxy groups have also been synthesized (10-13). Several of these also exhibit LCST's, as shown in Table I.[18] Presumably the LCST behavior of these polymers reflects a dominance by the "hydrophobic" character of the CH_2CH_2 units and the alkyl end units over the hydrophilic effect of the etheric oxygen atoms above the LCST. Replacement of a hydrophobic alkyl terminal group by a hydrophilic amino unit eliminates the LCST effect.

A characteristic of MEEP-type polymers is their low glass transition temperatures, which can be attributed to the combination of a highly flexible backbone and flexxible side groups. MEEP (5) itself has a T_g of -84°C, polymer 10 has a T_g of -75°C, and the values for 11 and 12 are -76°C and -84°C respectively. For 13, with a terminal NH_2 unit at each side group, the Tg rises to -18°C presumably because side group hydrogen bonding restricts the thermal motions of the macromolecules.

MEEP is of interest from several points of view. First, it is an excellent solid solvent for salts such as lithium triflate. The solid solutions function as solid polymeric ionic conductors and, as such, they have generated widespread interest as potential electrolytes in large area, lightweight, rechargeable lithium batteries (Figure 4).[19-22]

Second, MEEP can be crosslinked readily by exposure to gamma-rays or ultraviolet light.[23-25] The mechanism of this reaction, as illustrated in Scheme VII, is believed to involve C-H bond homolytic cleavage, followed by cross-combination of the resultant carbon radicals. The sensitivity of MEEP to radiation cross-linking is attributed to the presence of 22 C-H bonds on every repeating unit. Cross-linked MEEP swells in water to form stable hydrogels (Figure 4), the water content of which is a function of the degree of cross-linking. The cross-linking process has been used to entrap and immobilize enzymes with retention of enzymic activity[26]. Diffusion-release of small molecule solutes from the hydrogels has also been studied.[23]

Finally, radiation-cross-linked MEEP has been converted to swollen organogels by absorption of organic vinyl monomers (Figure 5). Polymerization and cross-linking of the organic monomers has yielded a range of interpenetrating polymer network (IPN) materials.[27] IPN's prepared with acrylonitrile and acrylic acid polymers show good component compatability, and this is consistent with the expected hydrophilic interactions. MEEP has also been used as the linear polymeric component in ceramic composites prepared via the sol-gel process, and these show a range of interesting and potentially useful properties.[28]

3. Polymers with Glucosyl Side Groups. Perhaps the ultimate in hydrophilic side group interactions might be expected from glucosyl units of the type shown in polymer **6**. With four free hydroxyl groups on every side group, the opportunities for H-bonding to water molecules would appear to be almost unprecedented in a synthetic polymer.

The synthesis of glucosyl-substituted polyphosphazenes presents a special challenge. Glucose itself has five functional sites per molecule, and any attempt to treat poly(dichlorophosphazene) with glucose would result in extensive cross-linking and polymer precipitation long before halogen replacement was complete. Thus, four of the five hydroxy units must be protected during coupling of the side group to the backbone, and must be deprotected during a final step. This process is shown in Scheme VIII.[29]

The second challenge is this: the protected diacetone glucose used in the initial macromolecular substitution is an exceedingly bulky nucleophile. Replacement of half the available chlorine atoms proceeds in a conventional manner. However, replacement of the remainder is slowed considerably by steric hindrance effects. Indeed, replacement of the last chlorine in a three repeat unit sequence appears to be exceedingly difficult, based on molecular graphics simulations (Figure 6), and it is not surprising that long reaction times and elevated reaction temperatures are needed for this final replacement.

Thus, from a practical point of view, it is easier to incorporate the glucosyl units as part of a mixed-substituent polymer, with the second nucleophile being less bulky than diacetoneglucoxide.[30] This is illustrated in Scheme IX.

A great deal of additional work needs to be done with sugar derivatives of polyphosphazenes, and this will undoubtedly occur as their biomedical properties are studied in more detail.

4. Glyceryl Derivatives. Glyceryl side groups offer similar opportunities for generating polymer water-solubility as was discussed for glucosyl units. Similar synthetic challenges are also encountered, especially with respect to the multifunctionality of glycerol and the need for protection-deprotection reactions. Steric hindrance is less of a problem. The synthesis sequence is shown in Scheme X.[31]

The glyceryl polymer, 14, is completely soluble in water. It has a glass transition temperature of 19.2°C.

5. Aryloxycarboxylic Acid Derivatives. Polymer 8 is an analogue of poly(acrylic acid) or of alginate macromolecules, from which it differs by the high concentration of carboxylate groups per repeating unit. It is of interest as a water-soluble polymer, as a polyelectrolyte, and as a biomedical encapsulant.

The synthesis of 8 requires the protection and eventual deprotection of the carboxylic acid function for the reasons discussed above.[32] The overall synthesis procedure is shown in Scheme XI. Although the parent polymer with carboxylic acid units is not soluble in water, the sodium and potassium salts have a high solubility in aqueous media.

Perhaps the most important property of the polymer is its ability to form ionic cross-links when the sodium salt is exposed to solutions of divalent or trivalent cations, such as Ca^{++} ot Al^{+++}. The ionically cross-linked materials are hydrogels, with the physical characteristics being determined by the divalent cation concentration. Infusion with solutions of monovalent cations reverses the process and leads to dissolution of the polymers. Preliminary tests have indicated that this polymer has a low oral toxicity.

The polymer has been studied as a species for the microencapsulation of biologically-active entities, such as mammalian cells, microorganisms, and proteins.[33-35] The microencapsulation procedure involves the dispersion of the biological entity in an aqueous solution of polymer 8 and expulsion of the bioactive species complete with a surrounding coating of polymer solution into an aqueous solution of calcium chlorate.

Liver hybridoma cells in culture, proteins, and immunostimulant species have been microencapsulated in this way. The bioerosion of the polymer has been induced by the incorporation of amino acid ester cosubstituent groups into the polymer.[36]

6. Polymers with Sulfonic Acid Solubilizing Groups. The polymer shown as **9** is representative of a range of structures with different ratios of aryloxy- and sulfonated aryloxy side groups. These are prepared by the sulfonation of poly[bis(phenoxy)phosphazene] (**15**), as shown in Scheme XII.[37] Relatively small amounts (>25%) of sulfonated aryloxy groups can induce water solubility. As discussed in the following section, sulfonation of the surface of an aryloxyphosphazene polymer can dramatically increase the hydrophilicity of the material. Sulfonated polyphosphazenes can also be prepared via two additional methods. First, it has been reported that the use of a sulfonated nucleophile in the primary macromolecular substitution process (Scheme II) yield polymers with aliphatic sulfonated units.[38] Second, we have shown recently that the reactions of aliphatic amino side groups with sultones generates sulfonated polyphosphazenes.[39]

Hydrolytic Stability.

As mentioned earlier, the stability or instability of a polymer to water will determine the applications, and especially the biomedical uses, for which it is suited. Two of the polymer classes discussed so far are sensitive to hydrolysis in neutral pH water at 100°C, (Table 2) and this reflects a much slower hydrolysis rate at body temperature. Thus, the glucosyl and glyceryl species hydrolyze slowly to phosphate, small amounts of ammonia, and glucose or glycerol. The biocompatibility of these products is obvious, and the utility of these systems in drug delivery and other biomedical applications is a subject of considerable interest. On the other hand, the methylamino-substituted polymer (**4**) and MEEP, are stable to water at neutral and basic pH, but are sensitive to strong acids.[40] The arylsulfonic acid-substituted polymers of type **9** appear to be stable to hydrolysis over a wide pH range. The hydrolysis behavior of the arylcarboxylic acid derivative (**8**) is still under investigation although, as mentioned

above, their hydrolysis can be induced by the presence of a hydrolytically sensitizing cosubstituent group.[36]

Hydrophilic Surfaces and Surface Hydrogels

Numerous needs exist in biomedicine for polymers that have a hydrophobic interior (to prevent water absorption and colonization by microorganisms) and a hydrophilic or hydrogel surface (Figure 7). Polyphosphazenes are particularly useful starting polymers for such materials because of (a) the wide range of side groups that can be employed, (b) the chemical stability of the skeleton, and (c) the possibilities that exist for the exchange of surface side groups by a variety of hydrophilic units.

A simple solution to this problem is shown in Figure 8. Here, films of poly[bis(trifluoroethoxy)phosphazene] (16) undergo replacement of surface fluoroalkoxy units by hydroxyl or $-O^- {}^+NBu_4$ units during treatment with aqueous solutions of sodium hydroxide containing tetrabutylammonium bromide - a phase transfer agent.[41] Hydrolysis proceeds rapidly from the surface generating an adhesive hydrogel as it penetrates toward the interior. The contact angle to water falls from 108° to 90° as the process takes place. Similar surface reactions have been used to link functional organic units to the surface of polyphosphazenes, as illustrated by Scheme XIII.[42]

A surface oxidation, as shown in Figure 9, converts p-methylaryloxy surface groups to units that bear carboxylic acid functions.[43] Again, the reaction is accompanied by a sharp decrease in contact angle from 92° to 70°, or to 25° in contact with basic media. Sulfonation of surface aryloxy groups, as in Figure 10, in the presence of sulfuric acid or SO_3 has a similar effect.[37]

These surface reactions are important because biomedical compatibility, particularly blood compatibility, depends on the hydrophilic character of the surface and on the absence or presence of ionic species. Considerable effort is being expended in

other laboratories to link poly- or oligoethylene oxide species to polymer surfaces in order to improve blood compatibility.[44] The thicker the hydrophilic layer (within limits), the more effective is the biological effect.

Recently, we have approached the same problem from a different point of view. As discussed, MEEP can be readily cross-linked by exposure to gamma-rays or ultraviolet light. This same radical-induced reaction also provides a mechanism for the covalent binding of MEEP to the surfaces of polymers such as polyethylene, polypropylene, or poly(vinyl chloride). The process is illustrated in Figures 11 and 12.[45] Evidence has also been obtained that MEEP hydrogels have some antibacterial activity[46] and this raises the possibility that the surface lamination process may be used to improve the resistance of polymeric biomaterials to colonization by microorganisms.

Concluding Comments

Within the field of macromolecules, relatively few polymers are soluble in water or are appropriate for conversion to hydrogels.[47] Proteins, nucleic acids, and some polysaccharides are obvious examples of species that are water-soluble, as are linear polyphosphates and polysilicates. However, for petrochemical polymers relatively few examples exist such as poly(ethylene oxide), poly(vinyl alcohol), poly(acrylic acid), poly(vinylpyrridine),and a variety of newer polymers that contain ether units in the backbone and hydroxy or carboxylate side units. [48]

The development of polyphosphazenes as water-soluble polymers and hydrogels offers many new possibilities in this field. These polymers have high molecular weights, have a hydrophilic backbone, have structures that can be varied over a wide range by the macromolecular substitution and cosubstitution routes and, when necessary, can be designed to be bioerodible. The six polymers shown as 4-9 represent the starting point

for work in this field. A much wider range of water-soluble structures can be anticipated as the structure-property relationships and uses become more extensively developed.

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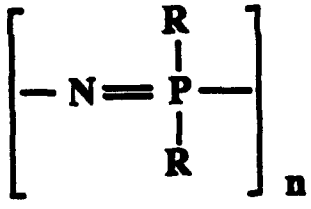

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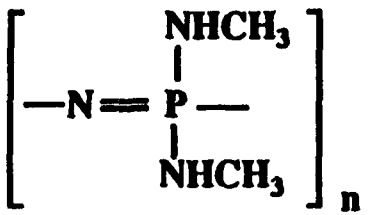
Chart 1. Water-Soluble Polyphosphazenes



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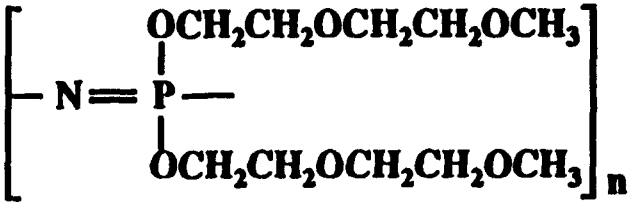

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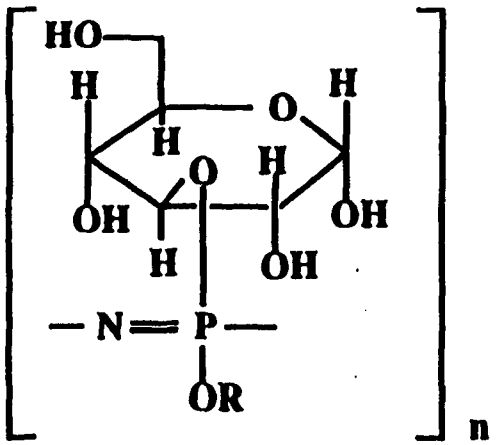

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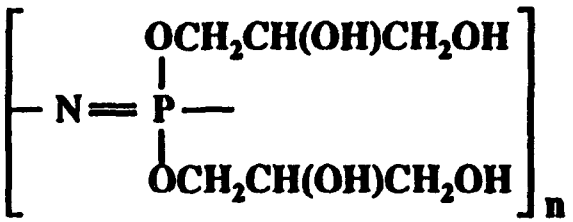

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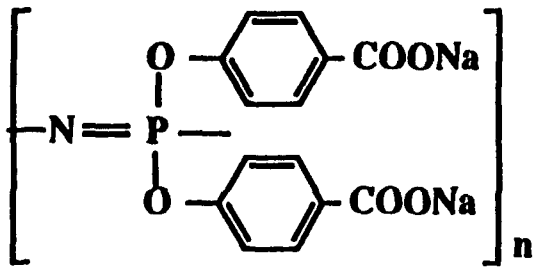

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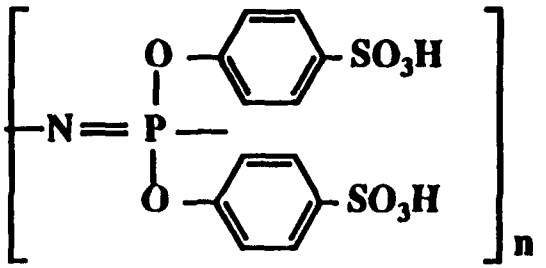
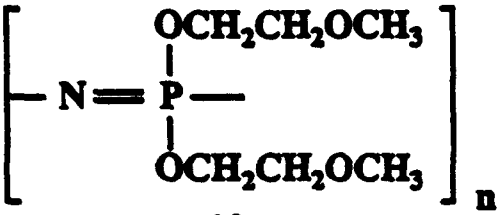
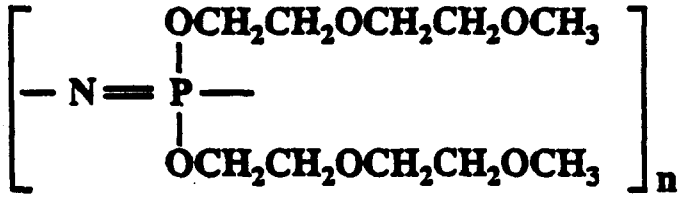
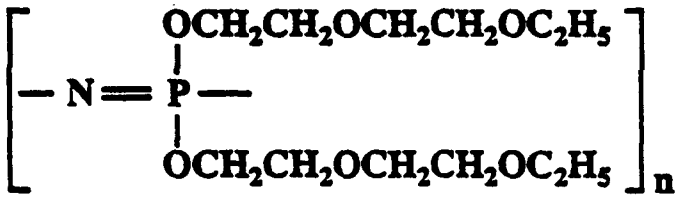
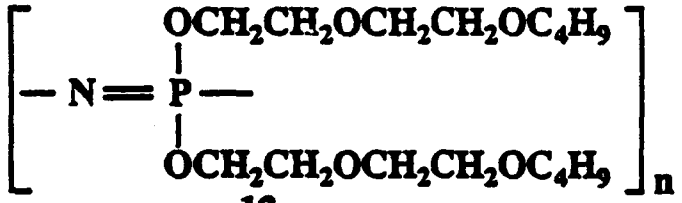
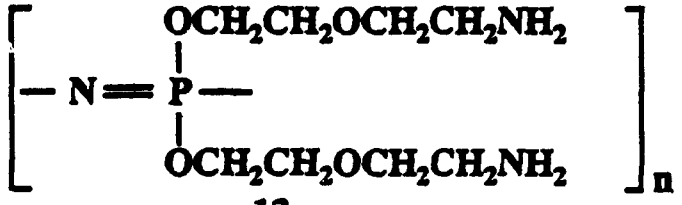


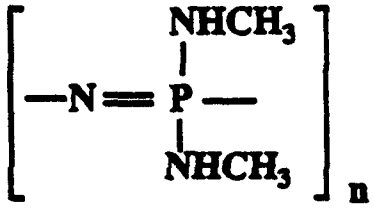
9

Table 1. LCST For MEEP and Related Polymers

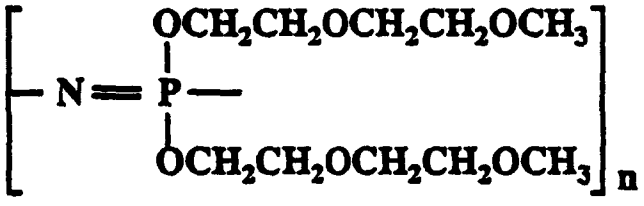
	Water Solubility at 25°C	LCST (°C)
 10	Sol.	30
 5	Sol.	80
 11	Sol.	38
 12	Sol.	51
 13	Sol.	None

Hydrogels Extrude Water at the Same Temperatures as the LCST

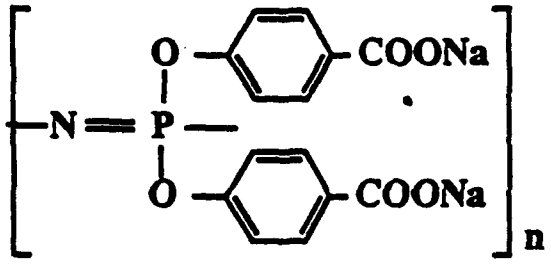
Table 2. Hydrolytic Sensitivity at pH 7 (Possible Bioerodibility)



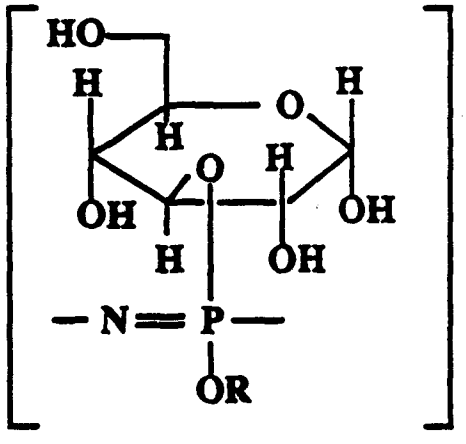
Stable



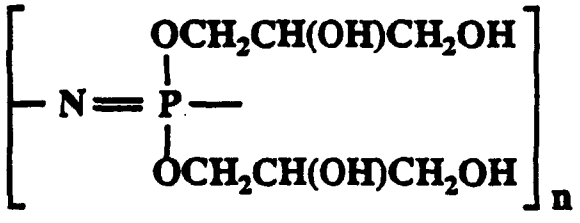
Stable



?



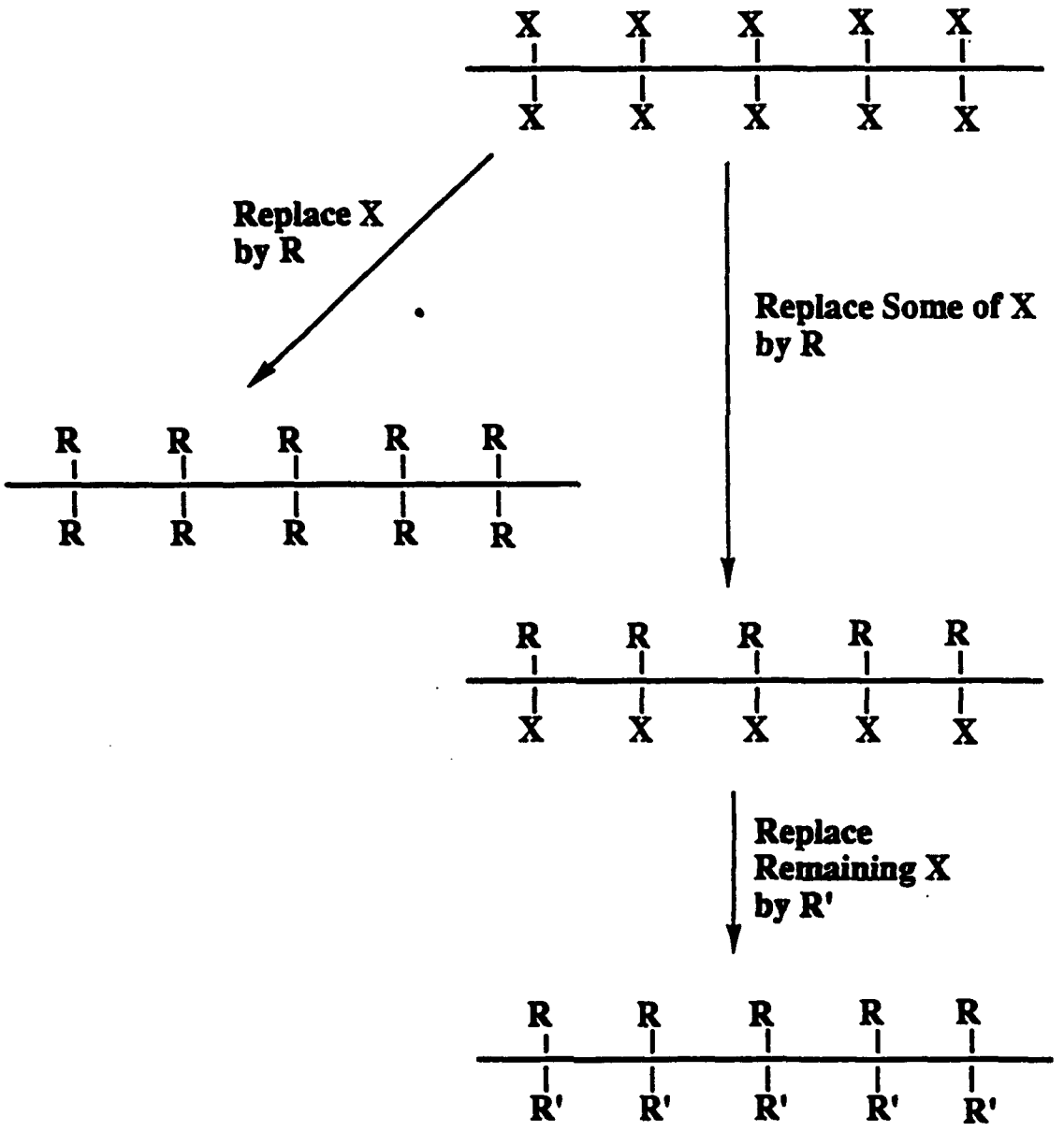
Hydrolyzes at 100°C to glucose, phosphate, ammonia, and ROH



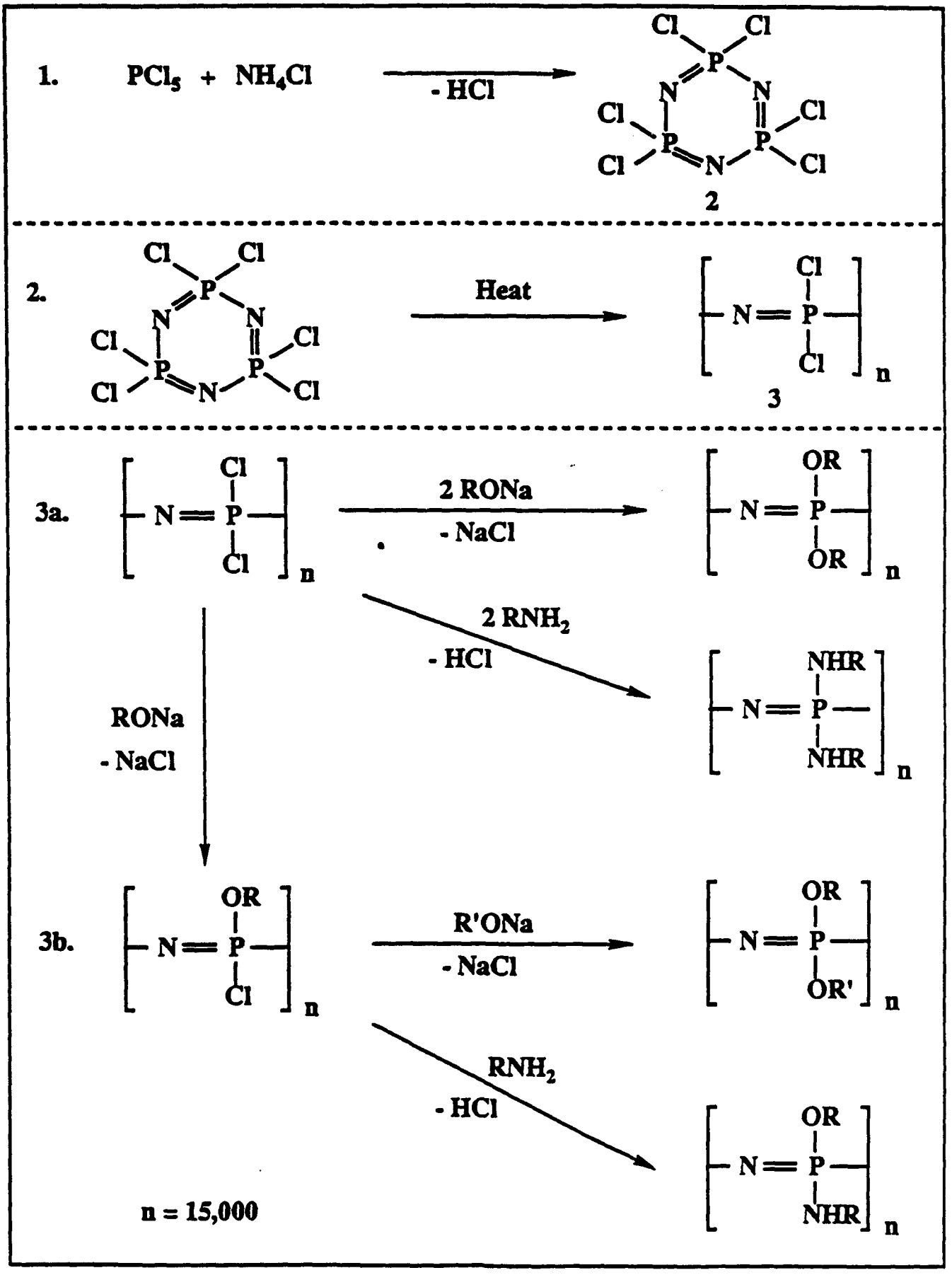
Hydrolyzes at 100°C to glycerol, phosphate, and ammonia

Scheme I

Macromolecular Substitution



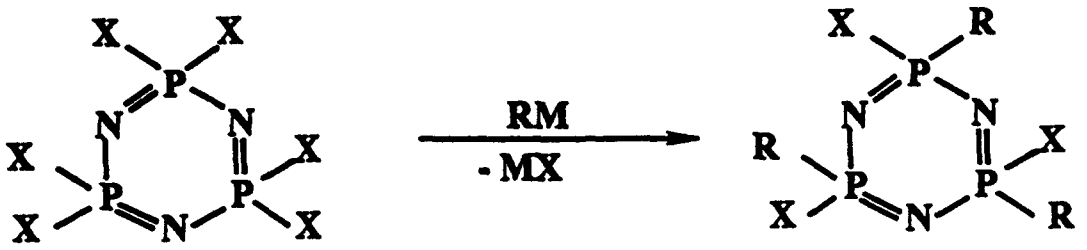
Scheme II


1. $PCl_5 + NH_4Cl$
- HCl
2
2.
Heat
3
3a.
2 RONa
- NaCl
2 RNH_2
- HCl
RONa
- NaCl
3b.
R'ONa
- NaCl
RNH_2
- HCl
n = 15,000

Scheme III

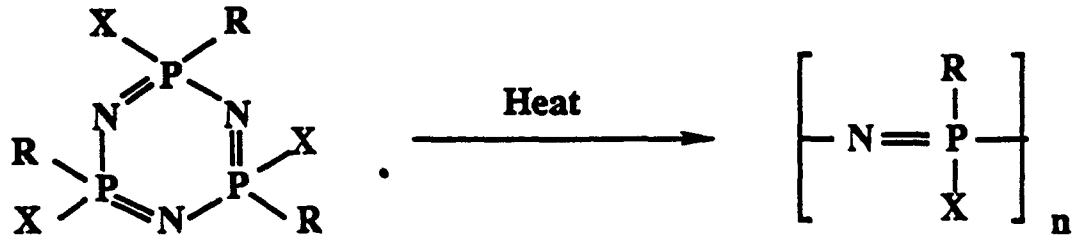
X = F or Cl

1.

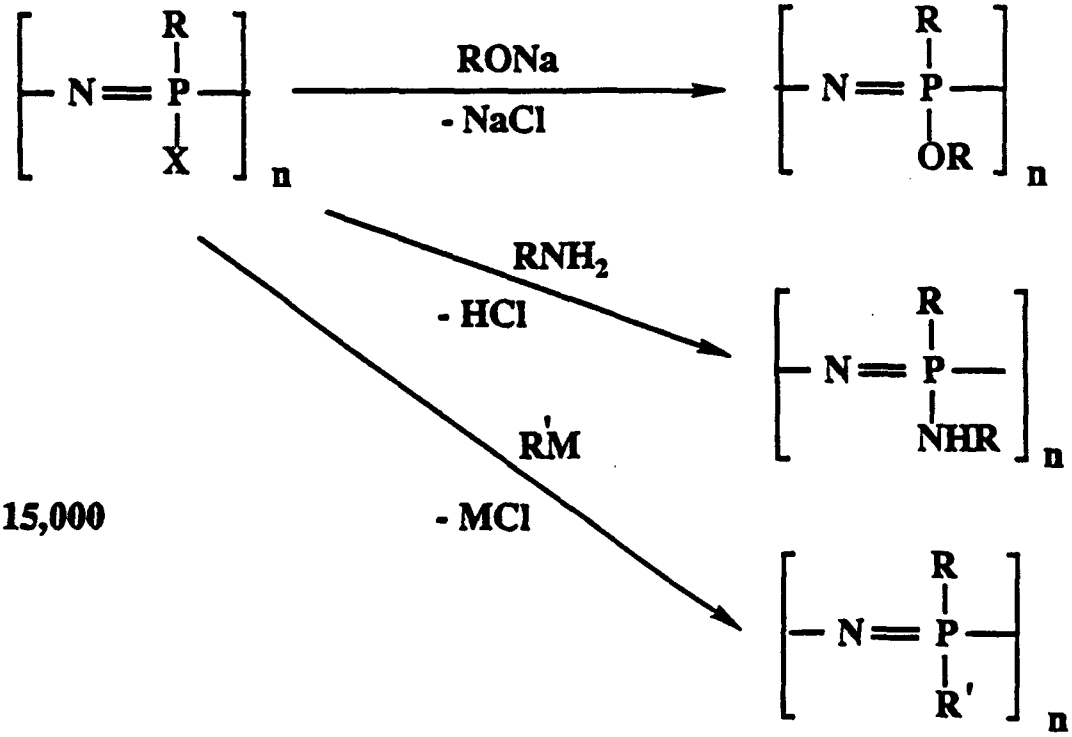


RM = Organometallic Reagent

2.

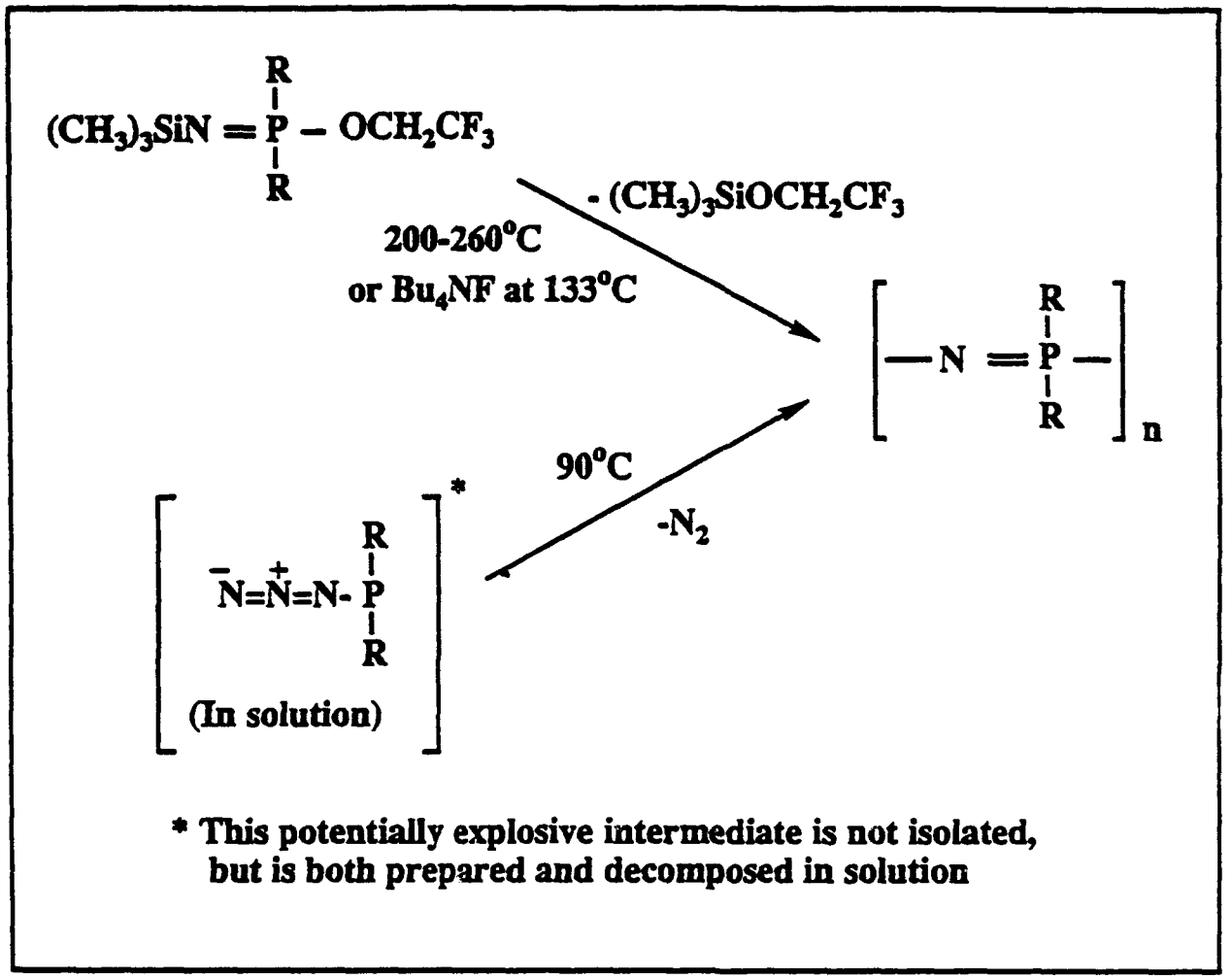


3.



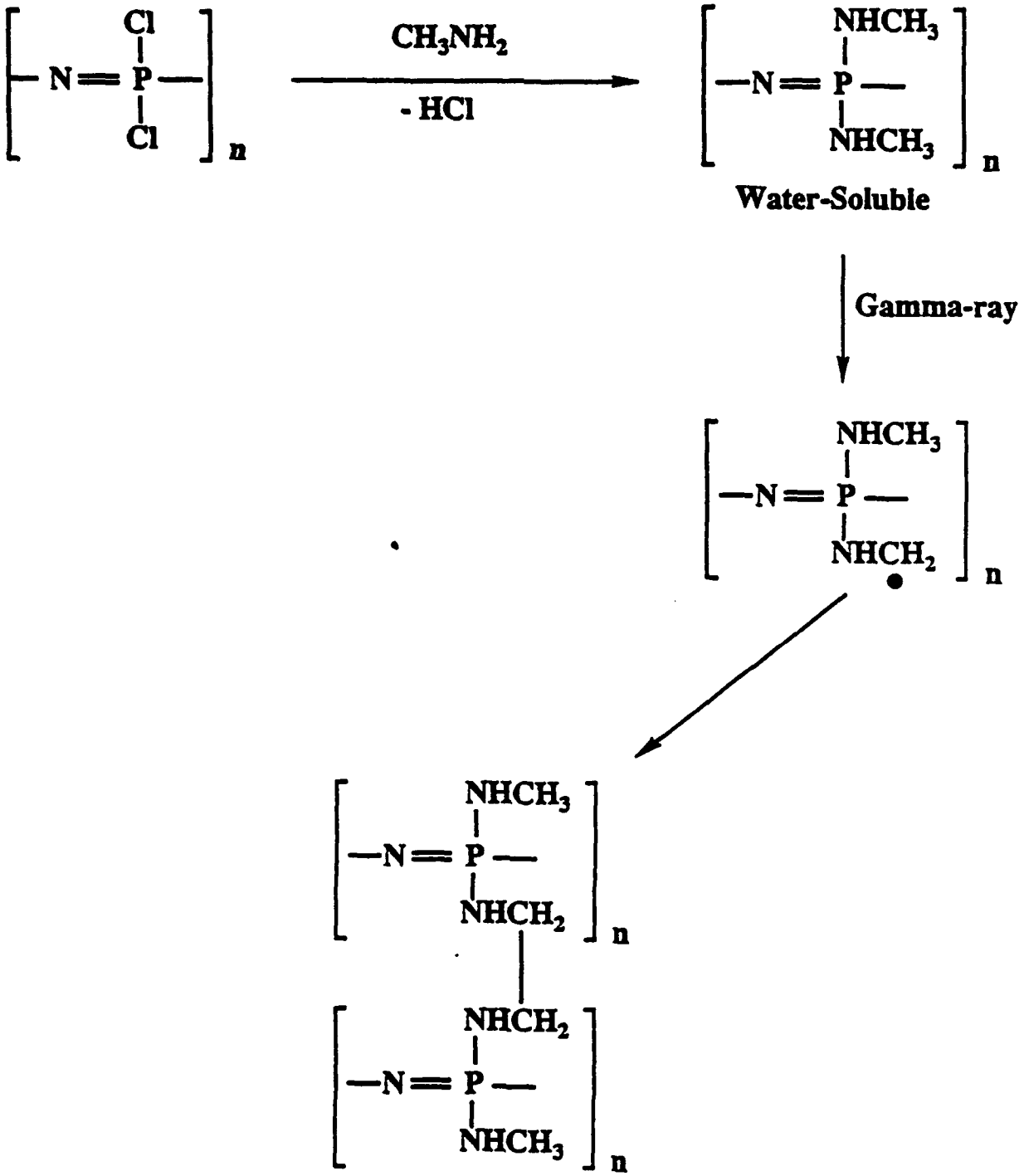
n = 15,000

Scheme IV

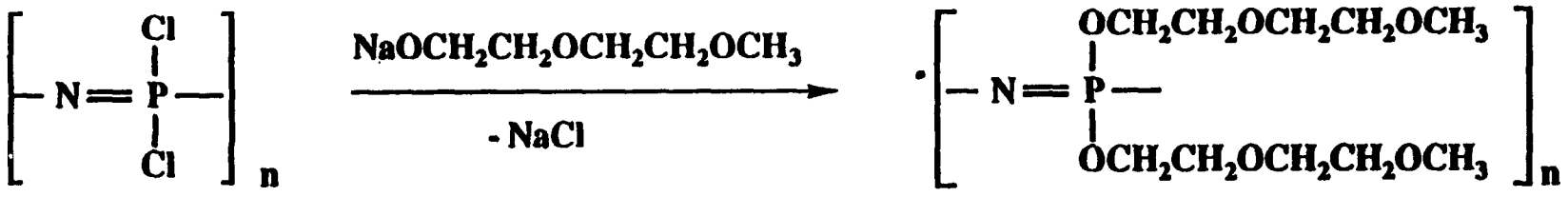


* This potentially explosive intermediate is not isolated, but is both prepared and decomposed in solution

Scheme V


Cl
N = P
Cl
n
CH3NH2
- HCl
NHCH3
NHCH3
Water-Soluble
Gamma-ray
NHCH2
NHCH2
NHCH3

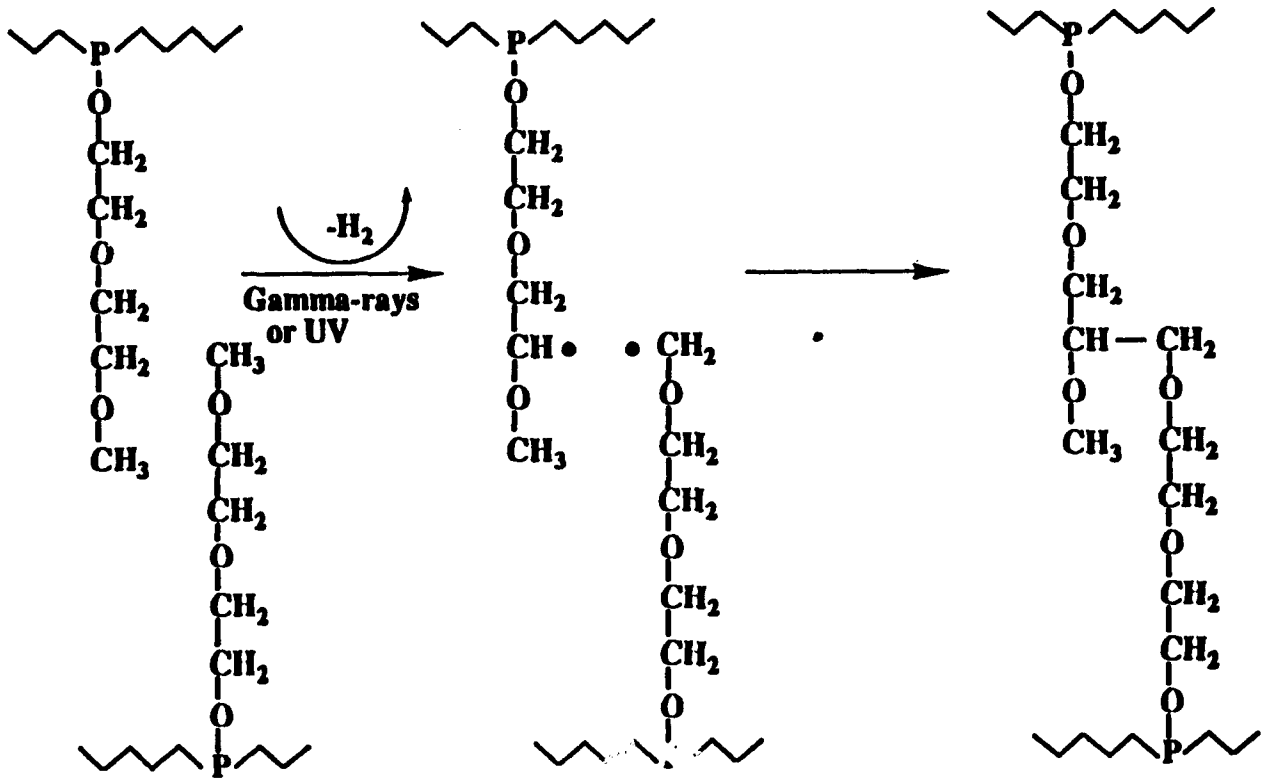
Scheme VI



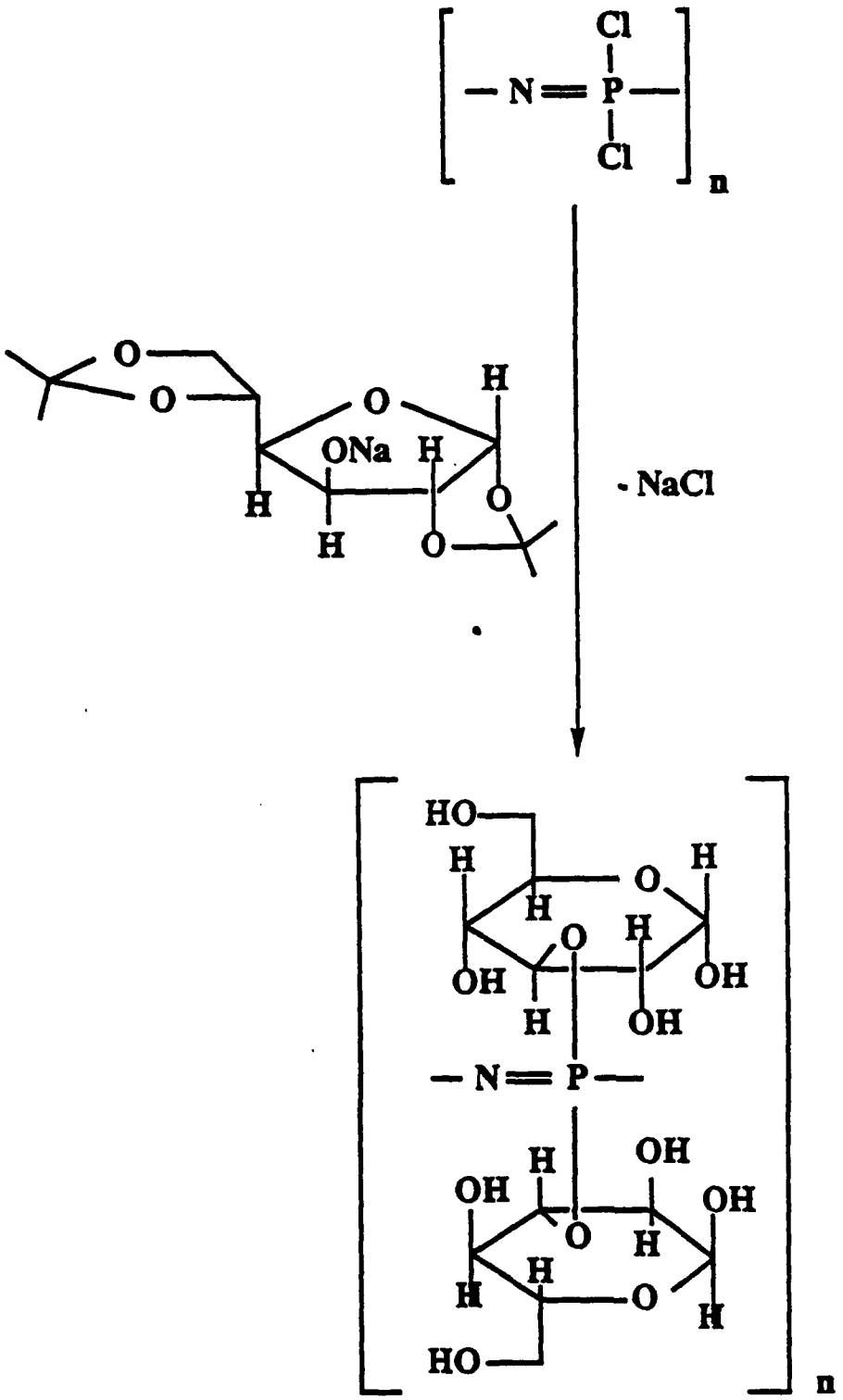
5

"MEEP"

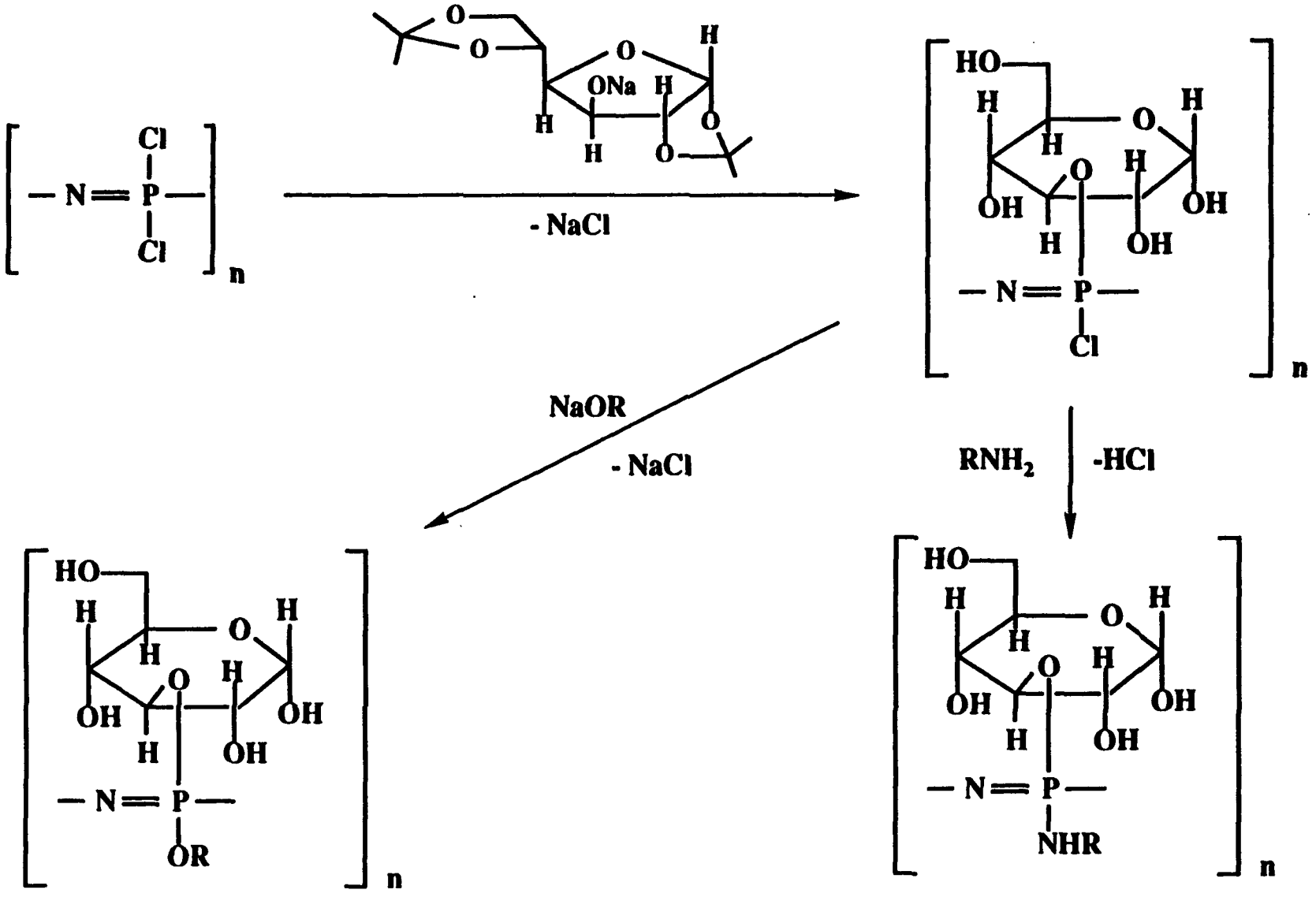
Scheme VII



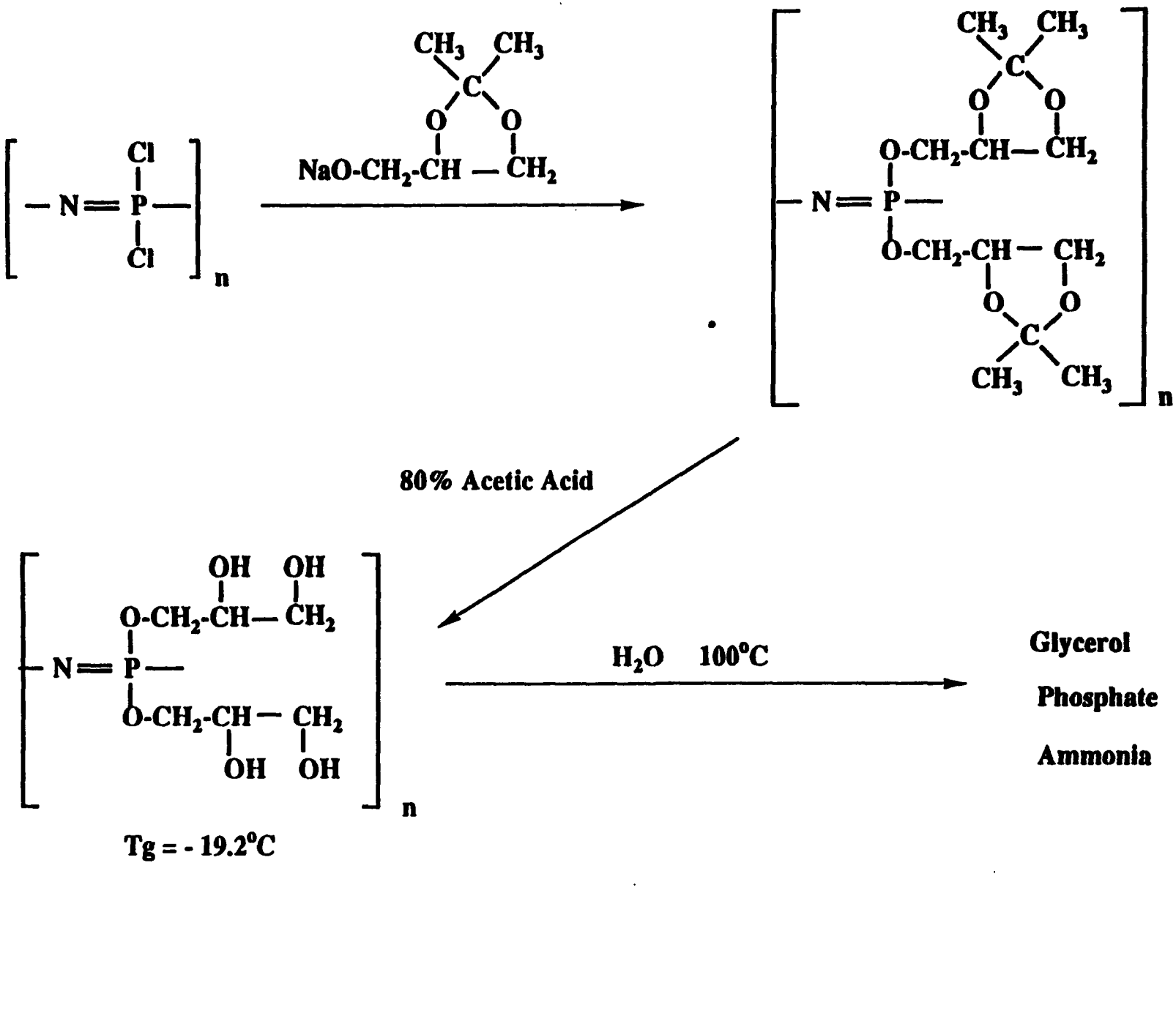
Scheme VIII


Cl
N
P
Cl
n
O
O
O
H
ONa
H
H
O
H
O
- NaCl
HO
H
O
H
H
O
H
OH
OH
H
OH
N
P
H
OH
OH
OH
O
H
H
H
O
H
HO
n

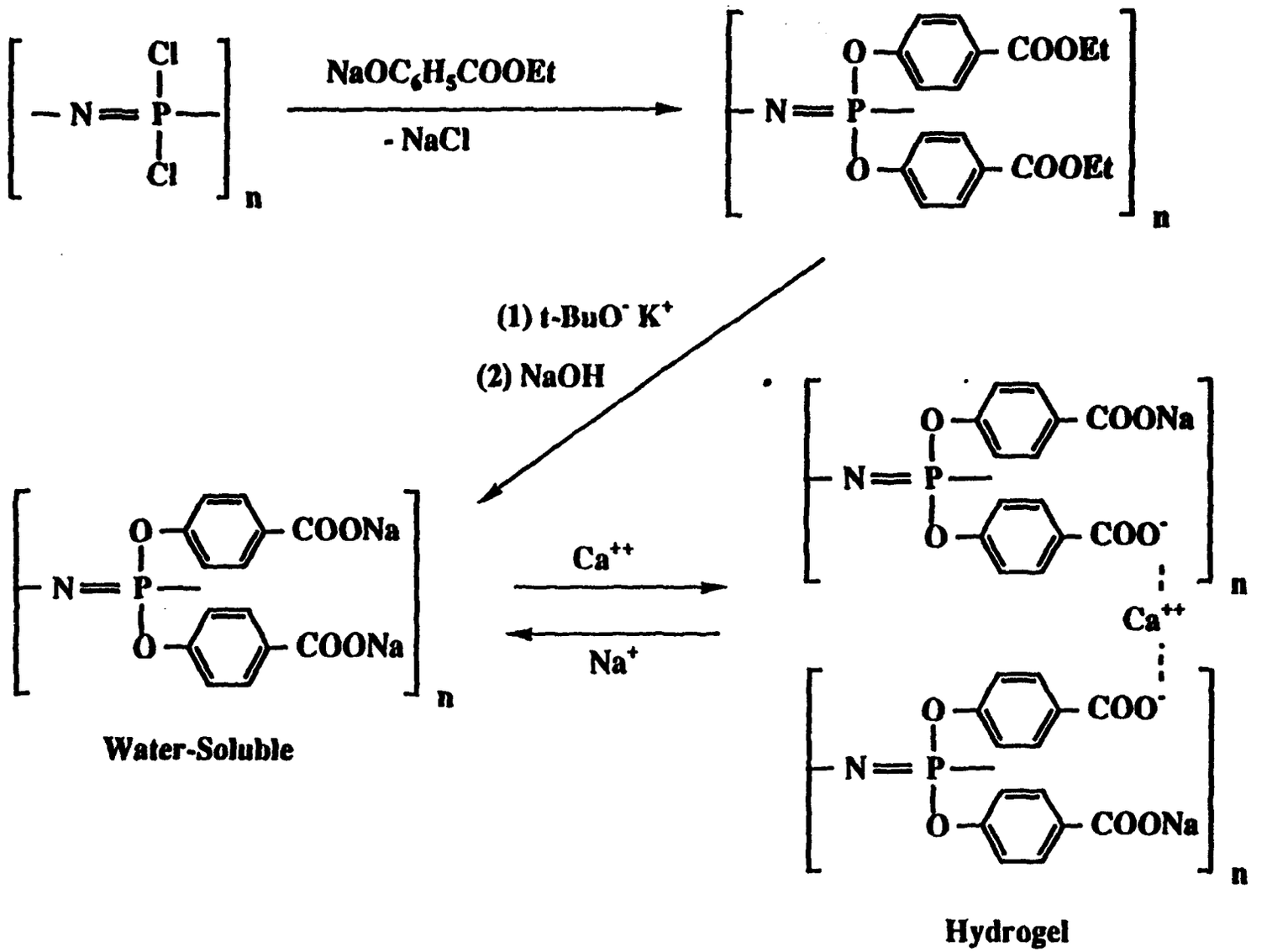
Scheme IX



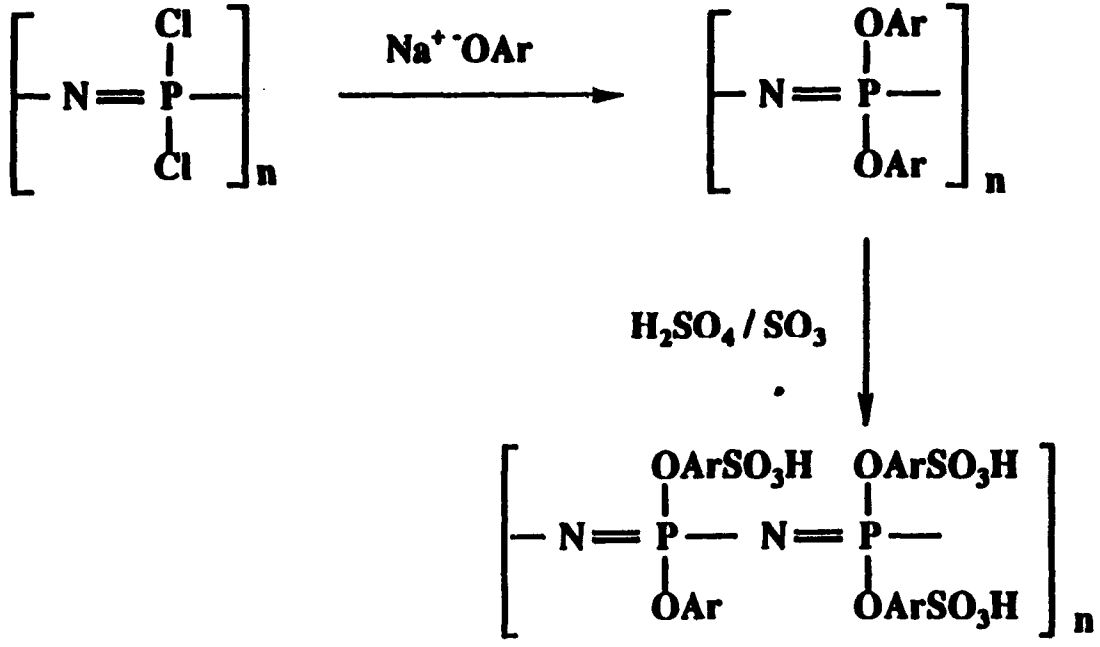
Scheme X


Cl
Cl
n
NaO-CH2-CH — CH2
CH3 CH3
O-CH2-CH— CH2
80% Acetic Acid
OH OH
H2O 100°C
Glycerol
Phosphate
Ammonia
Tg = - 19.2°C

Scheme XI


NaOC6H5COOEt
- NaCl
(1) t-BuO⁻ K⁺
(2) NaOH
Ca++
Na+
Water-Soluble
Hydrogel

Scheme XII



n = 2,000 to 7,000, or units at the surface of polymer films

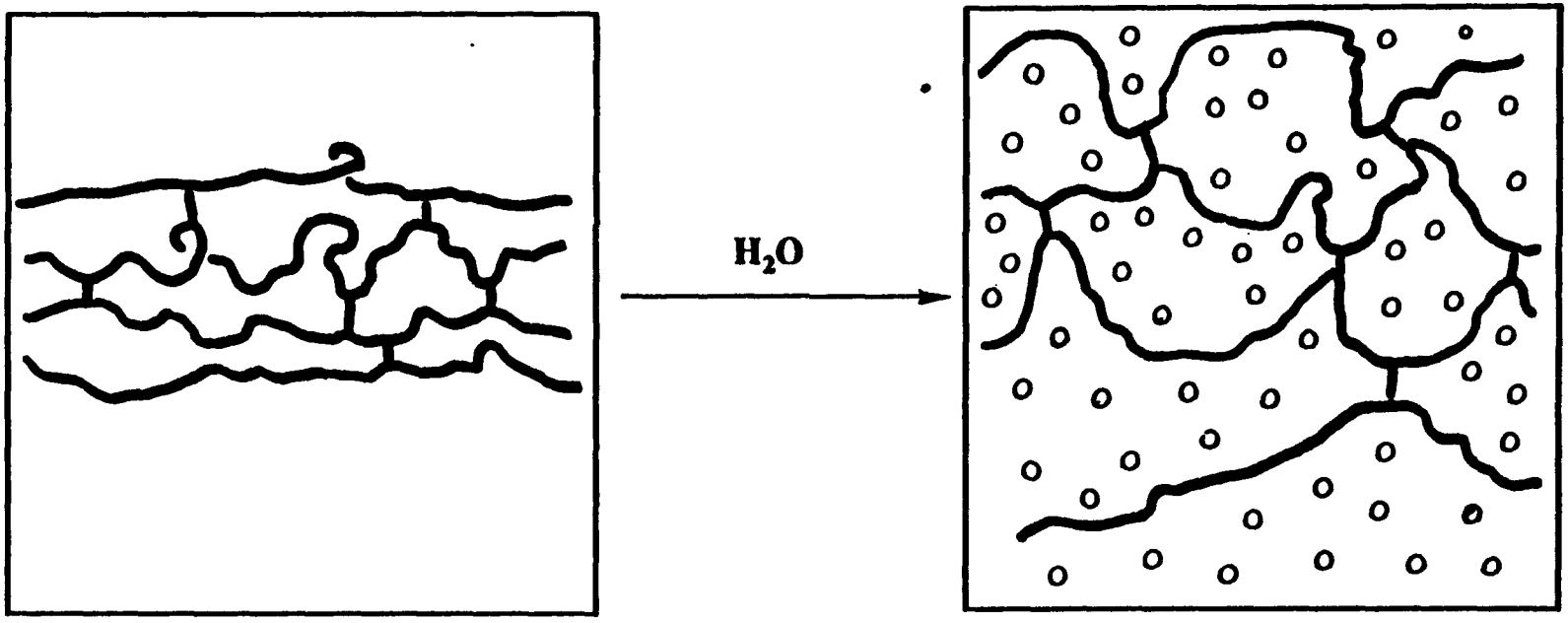


Figure 1. Crosslinking of water-soluble polymers generates hydrogels

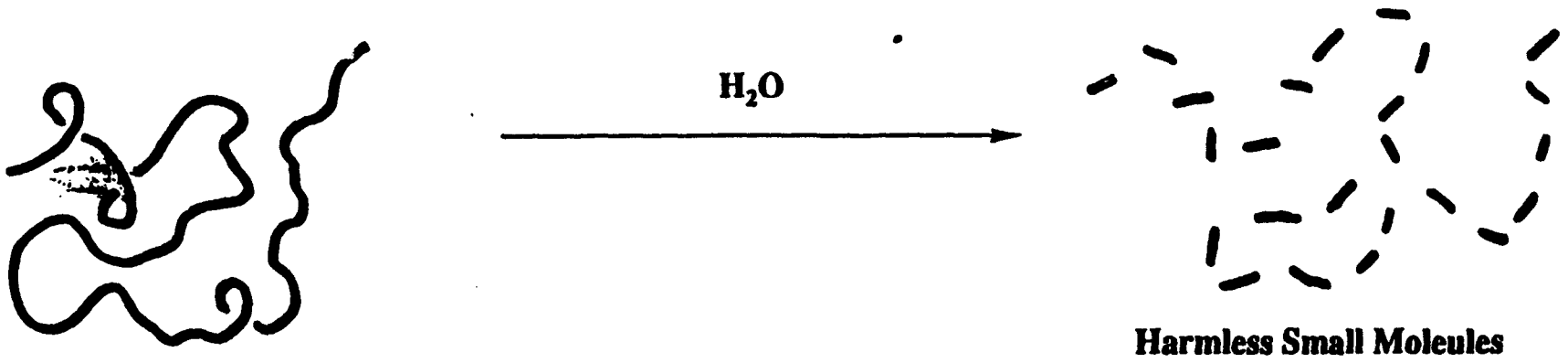


Figure 2. Hydrolytic instability may be utilized as bioerodibility

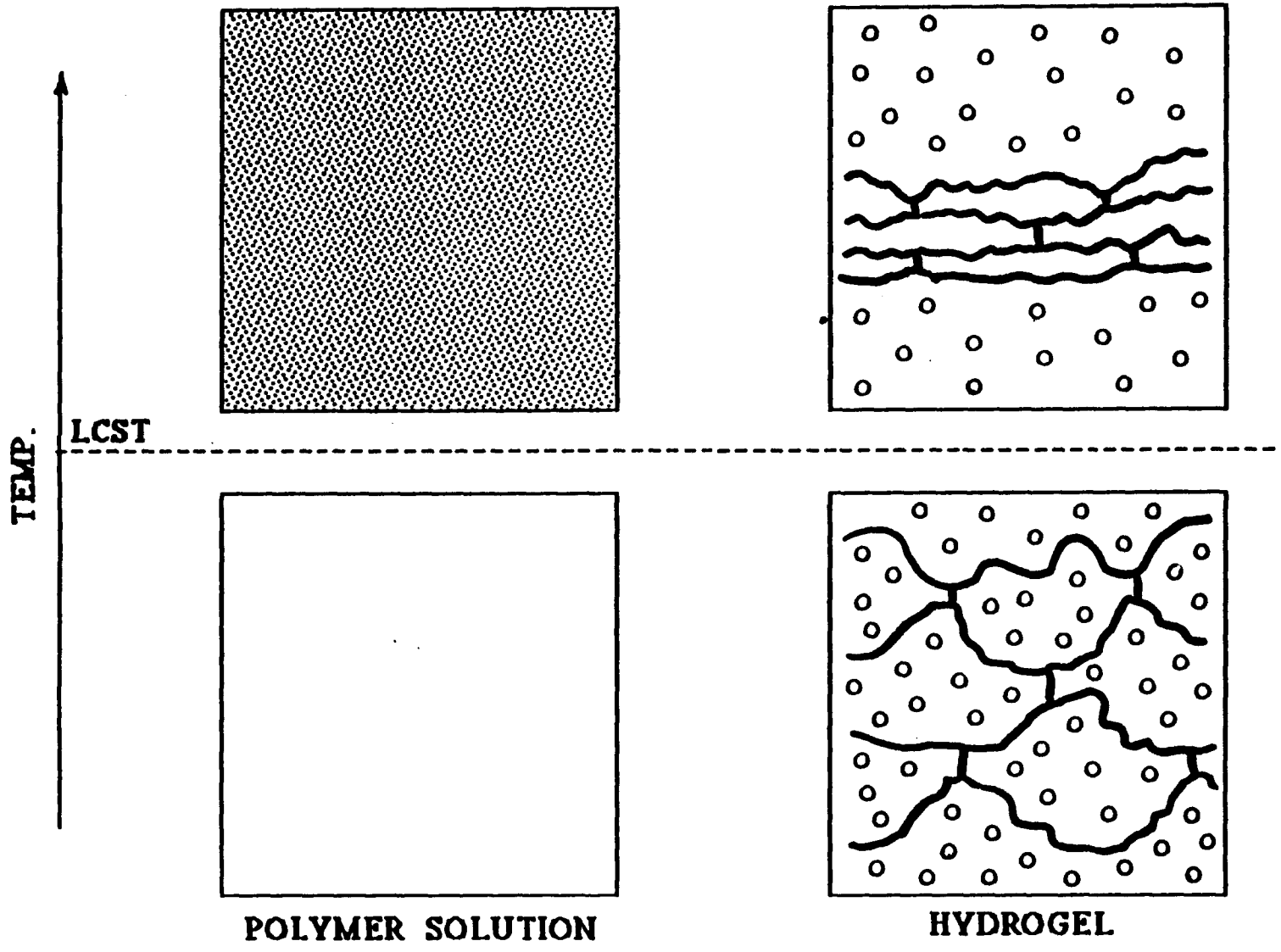


Figure 3. Lower critical solution temperature (LCST) for a polymer solution and hydrogel.

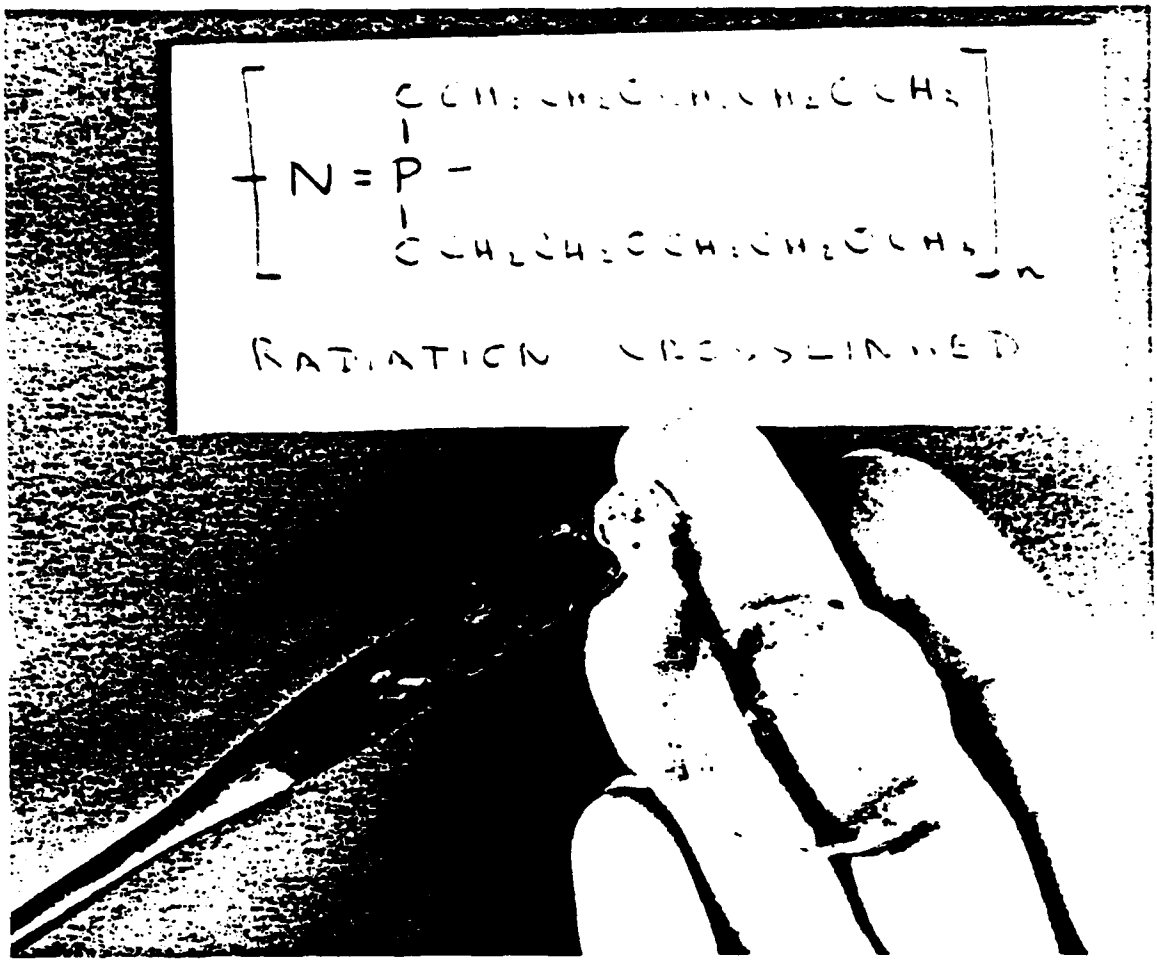


Figure 4. Poly[bis(methoxyethoxyethoxy)phosphazene], crosslinked by exposure to approximately 2 Mrad of gamma-rays, before and after immersion in water.

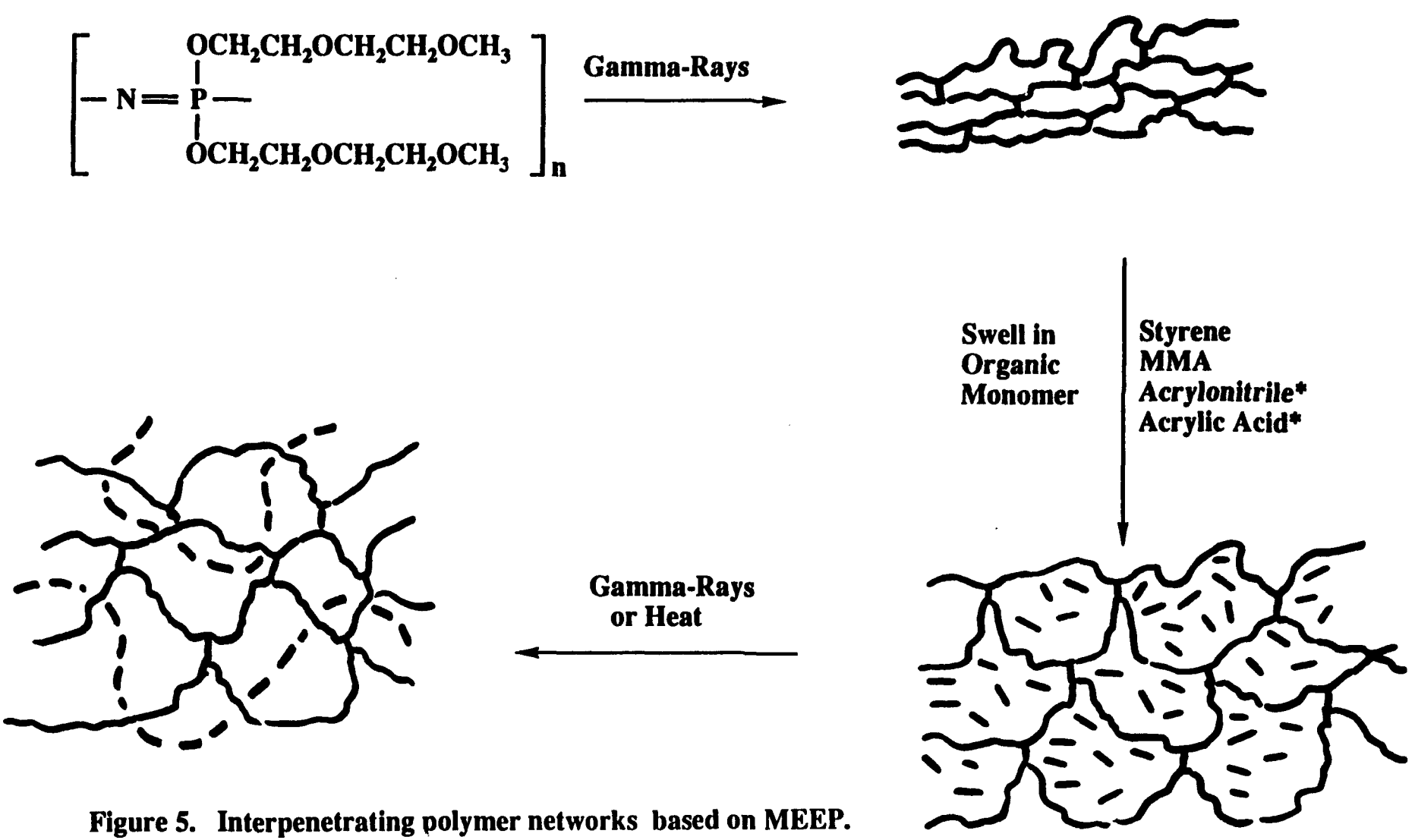


Figure 5. Interpenetrating polymer networks based on MEEP.

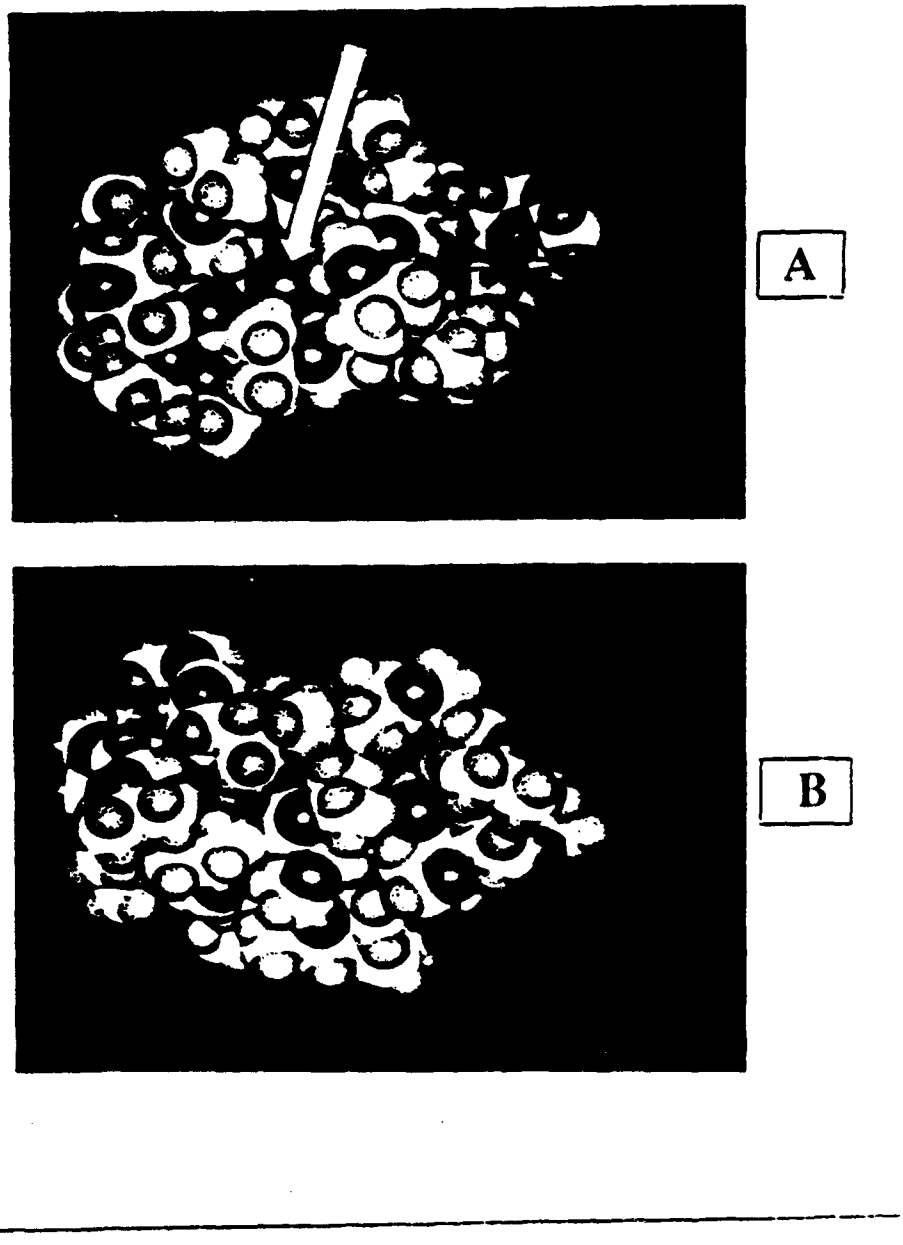


Figure 6. Molecular graphics simulation of (A) the steric hindrance involved in the replacement of the last chlorine atom (arrow) in a three-repeat unit segment of a polyphosphazene by a diactetone glucose anion, and (B) the close crowding that exists in a completely substituted segment of the chain.

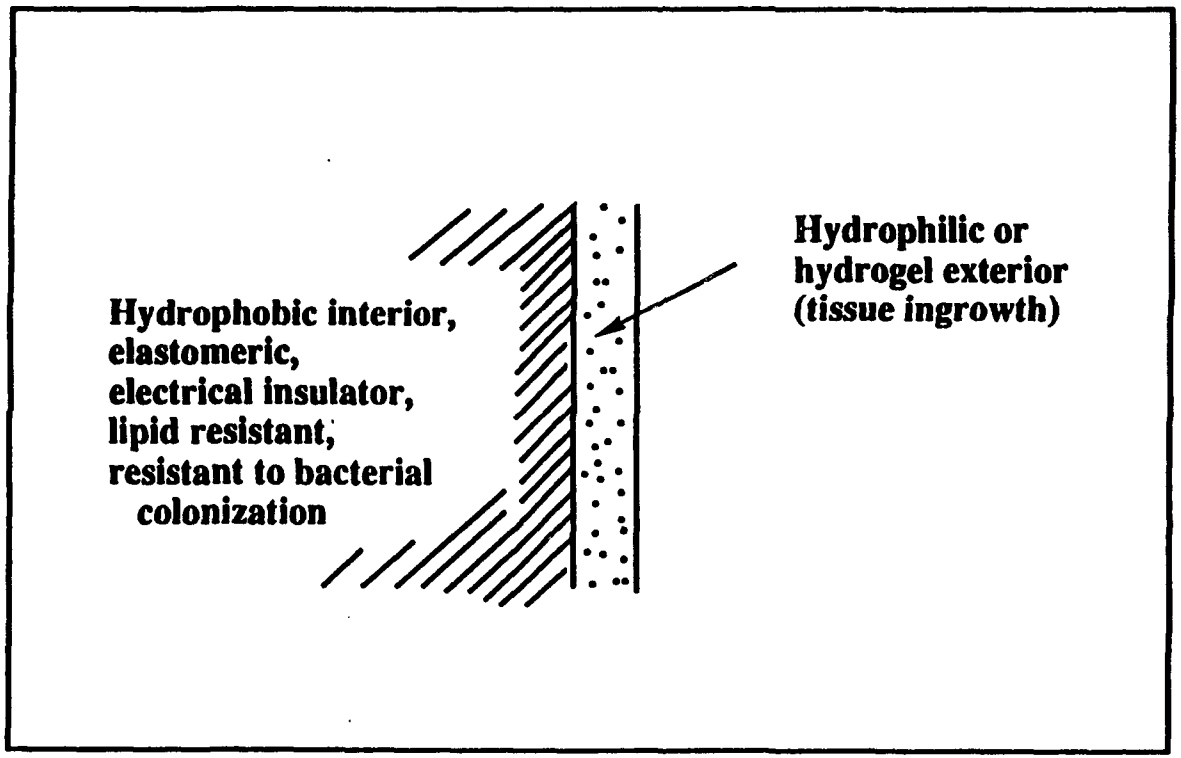


Figure 7. A target biomedical material.

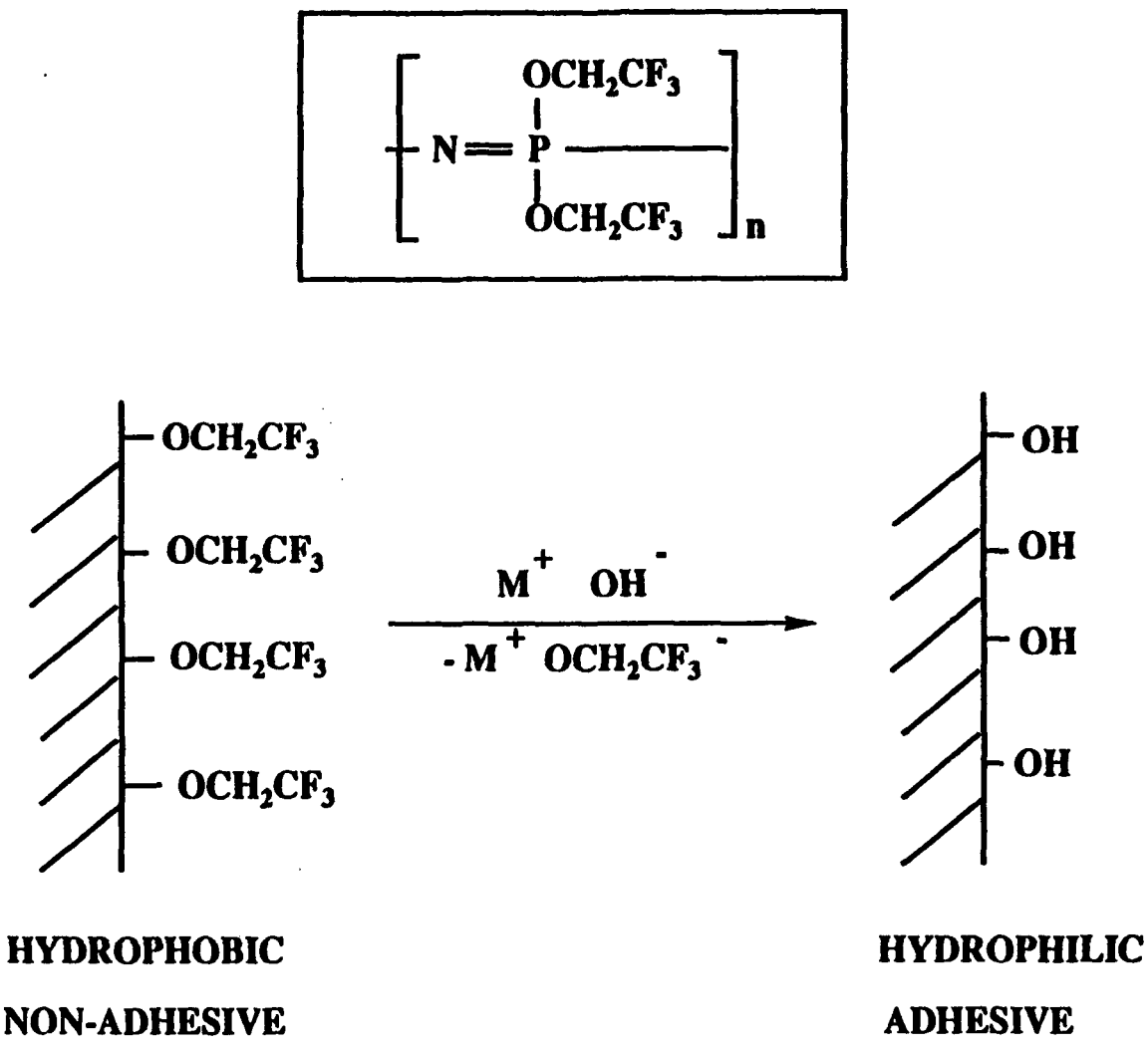


Figure 8. Treatment of the surface of poly[bis(trifluoroethoxy)-phosphazene with strong aqueous base in the presence of a phase-transfer reagent results in a change in surface character from hydrophobic to hydrophilic.

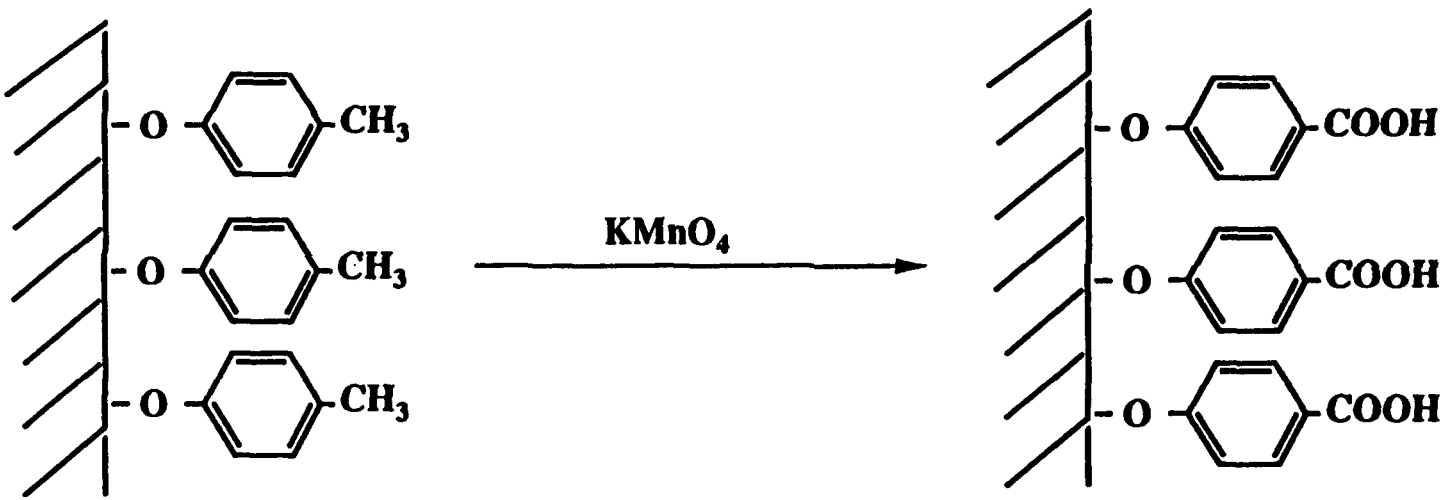


Figure 9. Oxidation of the surface of p-methylphenoxy groups linked to a polyphosphazene chain yields carboxylic acid surface units.

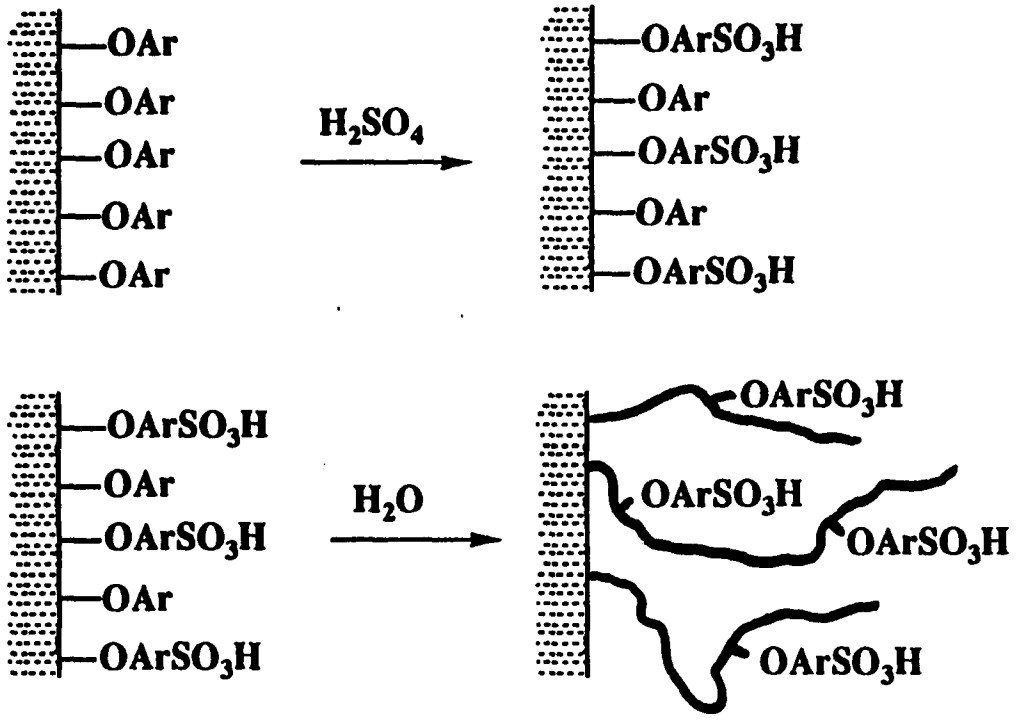
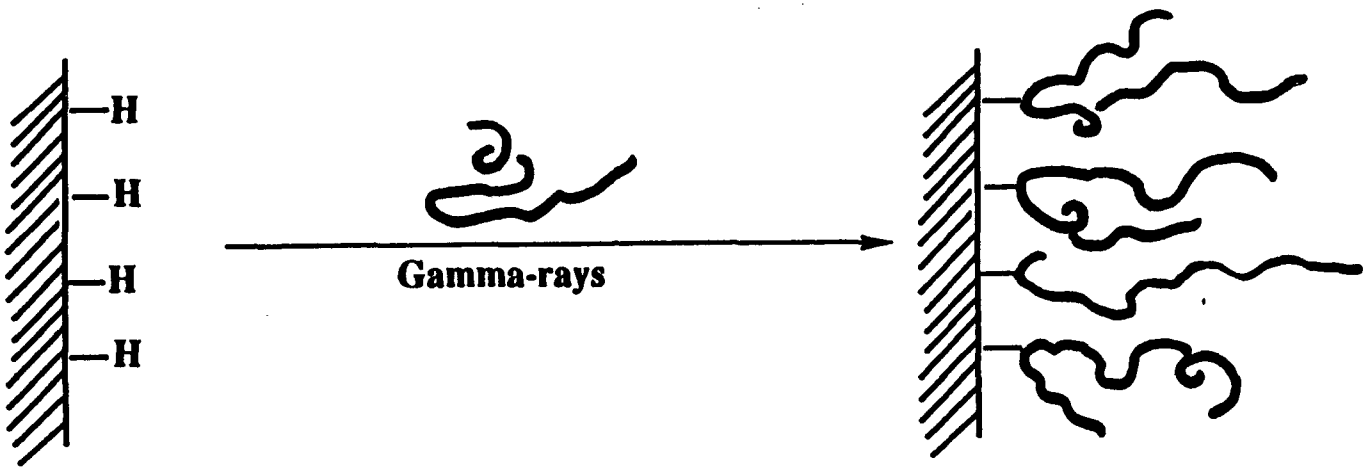
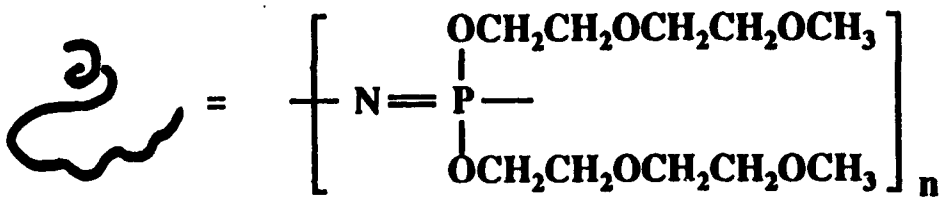


Figure 10. Sulfonation of the surface of poly[bis(aryloxy)phosphazenes], and expansion of the surface layer to form a hydrogel.





SUBSTRATE POLYMER (CONTACT ANGLE)		
POLYPROPYLENE	94°	27°
PVC	78°	34°
POLYCARBONATE	65°	43°
PMMA	65°	35°
MYLAR	63°	31°

Figure 11. Radiation grafting of molecules of poly[bis(methoxyethoxyethoxy)phosphazene] to the surface of a solid polymer, and the changes in contact angles to water that occur following grafting.[45]

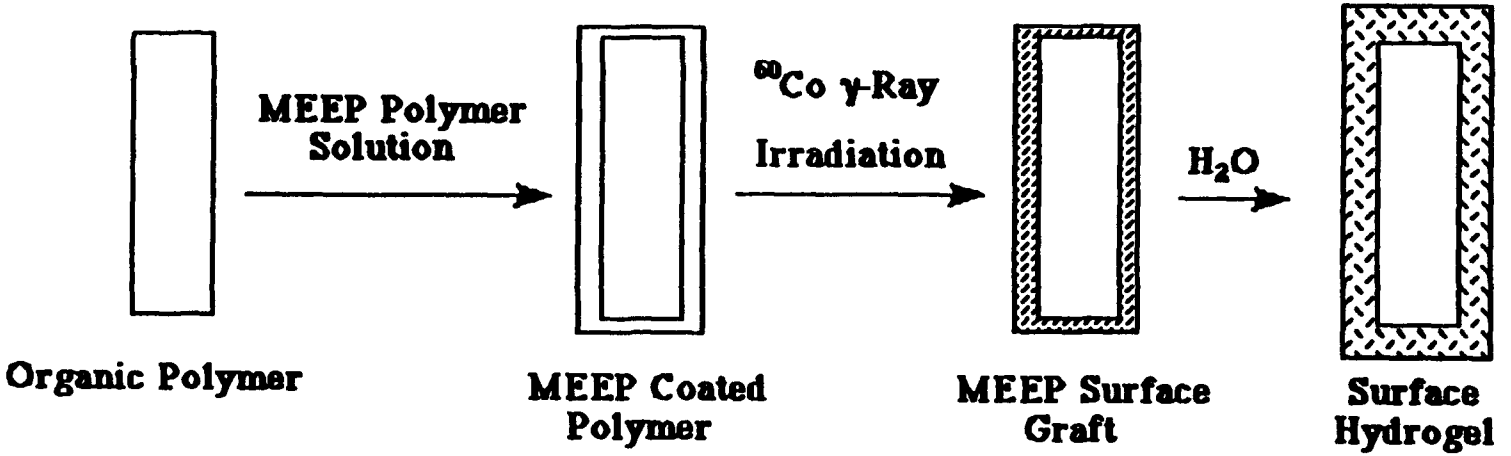


Figure 12. Generation of a hydrogel on the surface of an organic polymer following radiation-induced surface grafting of poly[bis(methoxyethoxyethoxy)phosphazene] (MEEP)

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